Claims

1. A vehicle for delivering a biologically active agent, comprising:
a poorly crystalline apatitic (PCA) calcium phosphate; and
a biologically active agent.

2. The vehicle of claim 1 wherein the PCA calcium phosphate has an X-ray diffraction pattern substantially as shown in Figure 5d.

3. The vehicle of claim 1 wherein the PCA calcium phosphate has an X-ray diffraction pattern comprising broad peaks at 2θ values of 26°, 28.5°, 32°, and 33°.

4. The vehicle of claim 1 wherein the PCA calcium phosphate has a calcium to phosphate ratio of less than about 1.5.

5. The vehicle of claim 1 wherein the PCA calcium phosphate is formulated so that when the vehicle compromises at least 1 g of PCA calcium phosphate, at least about 80% of the PCA calcium phosphate is resorbed within one year when the vehicle is placed in a rat intramuscular site.

6. The vehicle of claim 1 wherein the PCA calcium phosphate is formulated so that when the vehicle compromises at least 1 g of PCA calcium phosphate, at least about 80% of the PCA calcium phosphate is resorbed within 9 months when the vehicle is placed in a rat intramuscular site.

7. The vehicle of claim 1 wherein the PCA calcium phosphate is formulated so that when the vehicle compromises at least 1 g of PCA calcium phosphate, at least about 80% of the PCA calcium phosphate is resorbed within 6 months when the vehicle is placed in a rat intramuscular site.

8. The vehicle of claim 1 wherein the PCA calcium phosphate is formulated so that when the vehicle compromises at least 1 g of PCA calcium phosphate, at least about 80% of the PCA calcium phosphate is resorbed within 3 months when the vehicle is placed in a rat intramuscular site.

9. The vehicle of claim 1 wherein the PCA calcium phosphate is formulated so that when the vehicle compromises at least 1 g of PCA calcium phosphate, at least about 80% of the PCA calcium phosphate is resorbed within 1 month when the vehicle is placed in a rat intramuscular site.

10. The vehicle of claim 1 wherein the PCA calcium phosphate is formulated to be fully resorbable.

11. The vehicle of claim 1, wherein the PCA calcium phosphate material is formed from a hydrated precursor that is a paste.

12. The vehicle of claim 11, wherein the PCA calcium phosphate is formed from a hydrated precursor that is characterized by a tendency to harden at 22 °C after a time longer than one hour.

13. The vehicle of claim 11, wherein the PCA calcium phosphate is formed from a hydrated precursor that is characterized by a tendency to harden at 37 °C after a time shorter than one hour.

14. The vehicle of claim 11, wherein the PCA calcium phosphate is formed from a hydrated precursor that is characterized by a tendency to harden at 22 °C after about 10-30 minutes.

15. The vehicle of claim 1, further comprising an additional material selected to change a physical parameter of the vehicle, which physical parameter is selected from the group consisting of: strength, resorption time, adherence, injectability, frictional characteristics, and release kinetics.

16. The vehicle of claim 1 wherein the biologically active agent is selected from the group consisting of proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, and lipoproteins.

17. The vehicle of claim 1 wherein the biologically active agent is selected from the group consisting of anti-AIDS substances, anti-cancer substances, antibiotics, ACE inhibitors, adrenergic antagonists, antacids, immunosuppressants, anti-viral substances,

enzyme inhibitors, neurotoxins, opioids, hypnotics, antihistamines, lubricants, tranquilizers, anti-convulsants, muscle relaxants, anti-Parkinson substances, anti-spasmodics, muscle contractants, anti-diarrheals, anti-emetics, laxatives, diuretics, miotics, anti-cholinergics, anti-glaucoma compounds, anti-parasite compounds, anti-protozoal compounds, anti-hypertensives, analgesics, anti-pyretics, anti-inflammatory agents, anti-histamines, anti-tussive agents, anti-vertigo, antinertigic, anti-motion sickness medications, local anesthetics, ophthalmics, prostaglandins, anti-depressants, anti-psychotic substances, anti-emetics, imaging agents, specific targeting agents, trophic factors, growth factors, neurotransmitters, cell response modifiers, and vaccines.

18. A vehicle for delivering a biologically active agent, comprising:

a synthetic, poorly crystalline apatitic (PCA) calcium phosphate material having an X-ray diffraction pattern substantially as shown in Figure 5d; and

a biologically active agent.

19. A vehicle for delivering a biologically active agent, comprising:

a synthetic, poorly crystalline (PCA) apatitic calcium phosphate material characterized in that, when 1g of the material is placed in a rat intramuscular site, at least about 80% of the amount is resorbed within one year; and

a biologically active agent.

20. A vehicle for delivering a biologically active agent, comprising:

a synthetic, poorly crystalline apatitic (PCA) calcium phosphate material made from a process comprising:

exposing an amorphous calcium phosphate (ACP) to a promoter in the presence of a limited amount of an aqueous solution so that a hydrated precursor having a paste or putty consistency is formed; and

allowing the hydrated precursor to harden; and

a biologically active agent.

21. The vehicle of claim 20, wherein the promoter comprises a calcium source that participates in the conversion of the ACP to PCA calcium phosphate and is incorporated into the PCA calcium phosphate.

22. The vehicle of claim 21 wherein the calcium source is selected from the group consisting of CaO, $CaCO_3$, and calcium acetate.

23. The vehicle of claim 20 wherein the promoter comprises a phosphate source that participates in conversion of the ACP to PCA calcium phosphate and is incorporated into the PCA calcium phosphate.

24. The vehicle of claim 23 wherein the phosphate source comprises H_3PO_4.

25. The vehicle of claim 23 wherein the promoter further comprises a calcium source, the calcium source and phosphate source being selected and combined so that, in reaction with the ACP, they produce a PCA calcium phosphate with a Ca/P ratio within the range of approximately 1.1-1.9.

26. The vehicle of claim 20 wherein the promoter comprises a second calcium phosphate, selected to provide appropriate stoichiometry for reaction with the ACP to produce the PCA calcium phosphate.

27. The vehicle of claim 26 wherein the second calcium phosphate is selected from the group consisting of calcium metaphosphate, dicalcium phosphate dihydrate, heptacalcium decaphosphate, tricalcium phosphates, calcium pyrophosphate dihydrate, PCA calcium phosphate, calcium pyrophosphate, octacalcium phosphate, tetracalcium phosphate, and amorphous calcium phosphates.

28. The vehicle of claim 20 wherein the promoter is DCPD.

29. The vehicle of claim 20 wherein the promoter is stoichiometric hydroxyapatite.

30. The vehicle of claim 20 wherein the promoter is a granular material having an average grain diameter of approximately 1-200 μm.

31. The vehicle of claim 30 wherein the promoter is bioresorbable.

32. The vehicle of claim 30 wherein the promoter is selected from the group consisting of PLLA and PGA.

33. The vehicle of claim 20 wherein the promoter does not participate in conversion of ACP to the PCA calcium phosphate.

34. The vehicle of claim 33 wherein the promoter is a material selected from the group consisting of Al_2O_3, mica, glass, and sand.

35. The vehicle of claim 20 wherein the promoter is a treatment comprising heating the hydrated precursor.

36. The vehicle of claim 20, wherein the aqueous solution is a buffered solution selected for its compatibility with the biologically active agent.

37. The vehicle of claim 20, the vehicle being formed by a process comprising steps of:

mixing the ACP, the promoter, and the biologically active agent together in the presence of a buffered solution selected for its compatibility with the biologically active agent; and

allowing the mixture to harden.

38. The vehicle of claim 20, the vehicle being formed by a process comprising steps of:

mixing the reactive amorphous calcium phosphate and the promoter together in the presence of an aqueous solution, so that a hydrated precursor is formed;

allowing the hydrated precursor to harden; and

applying the biologically active agent to the poorly crystalline apatite calcium phosphate.

39. A vehicle for delivering a biologically active agent, comprising:

a synthetic, poorly crystalline apatitic calcium phosphate material made from a process comprising reacting an amorphous calcium phosphate (ACP) under conditions where crystal formation is inhibited, so that a poorly crystalline apatitic calcium phosphate is formed; and

a biologically active agent.

40. The vehicle of claim 39 wherein the ACP is reacted in the presence of a crystallization inhibitor.

41. A method of producing a vehicle for delivering a biologically active agent, the method comprising steps of:

providing a reactive amorphous calcium phosphate;

reacting the amorphous calcium phosphate with a material promoter in proportion to form a poorly crystalline apatitic calcium phosphate, the reaction being performed in an aqueous medium and in the presence of a biologically active agent, the aqueous medium being selected to preserve activity of the biologically active agent, so that the biologically active agent is incorporated into or onto the poorly crystalline apatitic calcium phosphate.

42. A method of producing a vehicle for delivering a biologically active agent, the method comprising steps of:

mixing in any order:

a reactive amorphous calcium phosphate (ACP);

a biologically active agent; and

a buffered aqueous solution selected for compatibility with the biologically active agent;

exposing the reactive ACP to a promoter before, after, or during mixing; and

allowing the mixture to harden after exposure to the promoter.

43. A method of producing a vehicle for delivering a biologically active agent, the method comprising steps of:

mixing in any order:

a reactive amorphous calcium phosphate (ACP); and

an aqueous solution;

adding a biologically active agent; and

exposing the reactive ACP to a promoter before, during, or after the mixing and adding steps,

so that the promoter promotes conversion of the ACP into a poorly crystalline apatitic (PCA) calcium phosphate.

44. The method of claim 43, wherein the step of mixing comprises mixing the reactive ACP with a material promoter in a buffered aqueous solution that is selected for its compatibility with the biologically active agent.

45. The method of claim 43, further comprising a step, performed either before or after the step of adding the biologically active agent, of:

allowing the mixture to harden.

46. The method of claim 43 further including a step of forming the PCA calcium phosphate into a predetermined shape.

47. The method of claim 43 further including a step of implanting the PCA calcium phosphate into a subject.

48. The method of claim 47 wherein the step of implanting comprises implanting in a site selected from the group consisting of bone, muscle, the spinal cord, the central nervous system, the interperitoneal cavity, a subcutaneous location, and the vitreous and aqueous humor of the eye.

49. A method of altering the resorbability kinetics of a poorly crystalline apatitic (PCA) calcium phosphate with altered bioresorbability, the method comprising steps of:

providing an amorphous calcium phosphate (ACP) in powder form;

providing a second calcium phosphate in powder form;

grinding the ACP or the second calcium phosphate to produce a powder with smaller grain size;

combining the ACP and the second calcium phosphate with a limited amount of an aqueous solution so that a hydrated precursor is formed; and

allowing the hydrated precursor to harden under conditions that result in formation of a PCA calcium phosphate.

50. The method of claim 49, wherein the step of combining comprises:

mixing the ACP and the second calcium phosphate;

grinding the mixture; and

adding the aqueous solution to the ground mixture.

51. A method of preparing a poorly crystalline apatitic (PCA) calcium phosphate with altered resorbability, the method comprising steps of:

providing an amorphous calcium phosphate (ACP);

providing a resorption modifier that comprises a material characterized either by an ability to resorb *in vivo* or by an ability to leach out of a PCA calcium phosphate;

combining the ACP with the resorption modifier;

exposing the ACP to a promoter before or after combination with the resorption modifier;

adding a limited amount of an aqueous solution to the ACP/material mixture, so that a hydrated precursor is formed;

allowing conversion of the hydrated precursor into a PCA material that incorporates the resorption modifier and that has a resorption profile different from that of an otherwise identical PCA material not incorporating the resorption modifier.

52. A therapeutic, structural, or cosmetic implant comprising:

a synthetic poorly crystalline apatitic (PCA) calcium phosphate; and

at least one cell.

53. The implant of claim 52 wherein the at least one cell is selected from the group consisting of chondrocytes, osteocytes, osteoblasts, osteoclasts, mesenchymal stem cells, fibroblasts, muscle cells, hepatocytes, parenchymal cells, cells of intestinal origin, nerve cells, and skin cells.

54. The implant of claim 52 wherein the at least one cell comprises at least one tissue-forming cell.

55. The implant of claim 54 wherein the at least one cell comprises at least one bone-forming cell.

56. The implant of claim 54 wherein the at least one cell comprises at least one cartilage-forming cell.

57. The implant of claim 52 wherein the at least one cell comprises a tissue-degrading cell.

58. The implant of any one of claims 55-57, wherein the at least one cell comprises a preparation selected from the group consisting of primary tissue explants, preparations of primary tissue explants, isolated cells, cell lines, transformed cell lines, and host cells.

59. The implant of claim 52 wherein the PCA calcium phosphate is strongly resorbable.

60. The implant of claim 59 wherein the PCA calcium phosphate has an X-ray diffraction pattern substantially as shown in Figure 5d.

61. The vehicle of claim 59 wherein the PCA calcium phosphate has an X-ray diffraction pattern comprising broad peaks at 2θ values of 26°, 28.5°, 32°, and 33°.

62. The vehicle of claim 59 wherein the PCA calcium phosphate has a calcium to phosphate ratio of less than about 1.5.

63. The vehicle of claim 59 wherein the PCA calcium phosphate is formulated so that when the vehicle compromises at least 1 g of PCA calcium phosphate, at least about 80% of the PCA calcium phosphate is resorbed within one year when the vehicle is placed in a rat intramuscular site.

64. The vehicle of claim 59 wherein the PCA calcium phosphate is formulated so that when the vehicle compromises at least 1 g of PCA calcium phosphate, at least about 80% of the PCA calcium phosphate is resorbed within 9 months when the vehicle is placed in a rat intramuscular site.

65. The vehicle of claim 59 wherein the PCA calcium phosphate is formulated so that when the vehicle compromises at least 1 g of PCA calcium phosphate, at least about 80% of the PCA calcium phosphate is resorbed within 6 months when the vehicle is placed in a rat intramuscular site.

66. The vehicle of claim 59 wherein the PCA calcium phosphate is formulated so that when the vehicle compromises at least 1 g of PCA calcium phosphate, at least about 80% of the PCA calcium phosphate is resorbed within 3 months when the vehicle is placed in a rat intramuscular site.

67. The vehicle of claim 59 wherein the PCA calcium phosphate is formulated so that when the vehicle compromises at least 1 g of PCA calcium phosphate, at least about 80% of the PCA calcium phosphate is resorbed within 1 month when the vehicle is placed in a rat intramuscular site.

68. The vehicle of claim 59 wherein the PCA calcium phosphate is formulated to be fully resorbable.

69. The vehicle of claim 59, wherein the poorly crystalline apatitic calcium phosphate material is formed from a hydrated precursor that is a paste.

70. The vehicle of claim 69, wherein the PCA calcium phosphate is formed from a hydrated precursor that is characterized by a tendency to harden at 22 °C after a time longer than one hour.

71. The vehicle of claim 69, wherein the PCA calcium phosphate is formed from a hydrated precursor that is characterized by a tendency to harden at 37 °C after a time shorter than one hour.

72. The vehicle of claim 69, wherein the poorly crystalline apatitic calcium phosphate is formed from a hydrated precursor that is characterized by a tendency to harden at 22 °C after about 10-30 minutes.

73. The vehicle of claim 69, wherein the PCA calcium phosphate is formed from a hydrated precursor that is characterized in that the hydrated precursor substantially hardens within about 15-40 minutes when placed *in vivo*.

74. The vehicle of claim 52, further comprising an additional material selected to change a physical parameter of the vehicle, which physical parameter is selected from the group consisting of: strength, resorption time, adherence, injectability, frictional characteristics, and release kinetics.

75. The vehicle of claim 52 further comprising a biologically active agent.

76. The vehicle of claim 75 wherein the biologically active agent is one that affects a process selected from the group consisting of cell growth, cell migration, cell differentiation, and cell localization.

77. The vehicle of claim 75 wherein the biologically active agent is selected from the group consisting of growth factors and extracellular matrix components.

78. The vehicle of claim 75 wherein the biologically active agent is selected from the group consisting of laminin, fibronectin, collagen, and combinations thereof.

79. The vehicle of claim 75 wherein the biologically active agent is selected from the group consisting of nutrients, angiogenic factors, and immunomodulatory factors.

80. The implant of claim 52 wherein the PCA calcium phosphate is prepared by a process comprising steps of:

providing an amorphous calcium phosphate (ACP);

exposing the ACP to a promoter;

forming a hydrated precursor from the ACP and a limited amount of aqueous solution, the amount of aqueous solution being selected so that the hydrated precursor has a consistency selected from the group consisting of a paste consistency and a putty consistency; and

allowing a conversion reaction in which the ACP is converted into a PCA calcium phosphate,

and the cells are added either before or after the step of allowing conversion.

81. The implant of claim 80 wherein the step of exposing comprises combing the ACP with a second calcium phosphate that participates in the conversion reaction and is selected to have appropriate stoichiometry so that the resultant PCA has a Ca/P ration within the range of 1.1-1.9.

82. The implant of claim 81 wherein the second calcium phosphate is selected from the group consisting of calcium metaphosphate, dicalcium phosphate dehydrate, heptacalcium decaphosphate, tricalcium phosphates, calcium pyrophosphate dehydrate,

PCA calcium phosphate, calcium pyrophosphate, octacalcium phosphate, tetracalcium phosphate, and amorphous calcium phosphates.

83. The vehicle of claim 81 wherein the promoter is DCPD.

84. The vehicle of claim 81 wherein the promoter is stoichiometric hydroxyapatite.

85. The implant of claim 81 wherein the promoter is selected from the group consisting of calcium sources, phosphate sources, and combinations thereof, the promoter being one that participates in the reaction and being selected for appropriate stoichiometry so that the resultant PCA calcium phosphate has a Ca/P ration in the range of approximately 1.1-1.9.

86. The implant of claim 80 wherein the step of exposing comprises combining the ACP with a promoter that does not participate in the conversion reaction.

87. The implant of claim 86 wherein the promoter is selected from the group consisting of Al_2O_3, mica, glass, sand, and heat.

88. The implant of claim 80 wherein the promoter is a granular material having an average grain diameter of approximately 1-200 μm.

89. The vehicle of claim 80 wherein the promoter is bioresorbable.

90. A method for preparing a therapeutic, structural or cosmetic implant, comprising:

a. providing a composition in hydrated precursor form, wherein the hydrated precursor is capable of conversion into a hardened PCA calcium phosphate;

b. promoting conversion of the hydrated precursor so that the composition becomes hardened PCA calcium phosphate;

c. before or after step b, introducing at least one cell into the composition.

91. The method of claim 90 wherein the step of providing comprises providing a hydrated precursor comprising:

a. an amorphous calcium phosphate (ACP) precursor;

b. a second precursor selected from the group consisting of: a calcium source, a phosphate source, combinations of calcium and phosphate sources, and calcium phosphates; and

c. a limited amount of an aqueous solution.

92. The method of claim 91 wherein the aqueous solution is a buffered solution selected for compatibility with the at least one cell.

93. The method of claim 91 wherein the cell is selected from the group consisting of chondrocytes, osteocytes, osteoblasts, osteoclasts, mesenchymal stem cells, fibroblasts, muscle cells, hepatocytes, parenchymal cells, cells of intestinal origin, nerve cells, and skin cells.

94. The implant of claim 53 wherein the at least one cell comprises at least one tissue-forming cell.

95. The implant of claim 83 wherein the at least one cell comprises at least one bone-forming cell.

96. The implant of claim 53 wherein the at least one cell comprises at least one cartilage-forming cell.

97. The implant of claim 53 wherein the at least one cell comprises a tissue-degrading cell.

98. The method of claim 39 wherein the step of introducing at least one cell comprises introducing a sufficient number of cells so that the PCA calcium phosphate is populated by at least about 20,000-1,000,000 cells/cm^3.

99. The method of claim 39, further comprising a step of shaping the hydrated precursor into a pre-determined form prior to hardening.

100. The method of claim 2, further comprising a step of shaping the hardened PCA calcium phosphate into a pre-determined form.

101. An *in vitro* cell culture system comprising:

a. a porous PCA calcium phosphate;

b. growth medium

c. at least one cell in or on the PCA calcium phosphate and in contact with the growth medium so as to be nourished thereby.

102. A method of growing bone *in vivo* comprising:

a. providing a hydrated precursor comprising:

i. at least one amorphous calcium phosphate (ACP);

ii. at least one bone-forming cell; and

iii. a sufficient amount of aqueous solution so that the hydrated precursor has a consistency selected from the group consisting of a paste consistency and a putty consistency, the aqueous solution being compatible with the at least one bone-forming cell;

b. introducing the hydrated precursor into a bony site; and

c. allowing the hydrated precursor to harden.

103. A method of growing bone *in vivo* comprising:

a. providing a hydrated precursor comprising:

i. at least one amorphous calcium phosphate (ACP); and

ii. a sufficient amount of aqueous solution so that the hydrated precursor has a consistency selected from the group consisting of a paste consistency and a putty consistency;

b. introducing the hydrated precursor into a bony site;

c. promoting conversion of the ACP into a PCA calcium phosphate before or after the step of introducing; and

d. allowing bone-forming cells to enter the implanted material.

104. A method of growing cartilage *in vivo* comprising:

a. providing a hydrated precursor comprising:

i. at least one amorphous calcium phosphate (ACP);

ii. at least one cartilage-forming cell; and

iii. a sufficient amount of aqueous solution so that the hydrated precursor has a consistency selected from the group consisting of a paste consistency and a putty consistency, the aqueous solution being compatible with the at least one cartilage-forming cell;

b. introducing the hydrated precursor into a site *in vivo*; and

c. allowing the hydrated precursor to harden.

105. A method of growing cartilage *in vivo* comprising:

a. providing a hydrated precursor comprising:

i. at least one amorphous calcium phosphate (ACP); and

ii. a sufficient amount of aqueous solution so that the hydrated precursor has a consistency selected from the group consisting of a paste consistency and a putty consistency;

b. introducing the hydrated precursor into a site *in vivo*;

c. promoting conversion of the ACP into a PCA calcium phosphate before or after the step of introducing; and

d. allowing cartilage-forming cells to enter the implanted material.

106. The method of claim 53 wherein the hydrated precursor further comprises a biologically active agent that attracts cartilage-forming cells so that, after implantation, cartilage-forming cells migrate into the implanted material.

107. A method of detecting a disease state in a host, the method comprising steps of:

a. providing a composition in hydrated precursor form, the composition comprising:

i. at least one amorphous calcium phosphate (ACP)

ii. a limited amount of an aqueous solution, the amount being selected so that the hydrated precursor has a consistency selected from the group consisting of paste consistent and putty consistency;

b. promoting conversion of the ACP to a PCA calcium phosphate;

c. before or after step b, introducing one at least one cell isolated from a host into the composition;

d. culturing the at least one cell in the composition under conditions in which analogous cells isolated from a healthy host form tissue; and

e. detecting a difference in capacity to form tissue in the cultured at least one cell as compared with analogous cultures cells isolated from a healthy host.